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(54) IMPROVEMENTS RELATING TO INJECTION DEVICES

VERBESSERTE INJEKTIONSVORRICHTUNGEN

AMELIORATIONS APPORTEES A DES DISPOSITIFS D'INJECTION

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Description

[0001] This invention relates to injection devices.

[0002] Often, when a sequence of injections is carried out, each time the entire contents of a capsule are ejected through the needle in a single stroke of a plunger. However, there are other circumstances where only a small amount of fluid should be used, and it is not always practical or economic to make a number of very small capsules and injection devices to cater for this. There is therefore a need for an injection device which can produce repeated measured doses from a single capsule.

[0003] DE-A-3638984 describes an injection device in which the dose to be administered can be set, the device 'fired', the needle replaced, and the device re-primed, if desired with a different setting for the dose. The cycle can be repeated until the syringe is exhausted or has insufficient for another shot. The sophistication of being able to adjust the dose leads to a complicated construction. The adjustment is done by a wheel which is rotated through a number of "clicks" corresponding to the size of dose required, and then by an adjacent knob which is rotated, until stopped at a position determined by the wheel, to screw forwards a plunger that will actuate the syringe. This is done with the device primed, the member into which the plunger screws being retracted against a powerful spring and held by a trigger clip mounted next to the dosage setting wheel. DE-A-3715258 describes a similar device.

[0004] There is clearly a risk, due to the proximity of the dose setting elements and the trigger clip, that the device will be fired prematurely, while the user is trying to set it up. But in practice such elaboration is not always necessary. Most injections are repeats of previous ones, the same dose being administered each time.

[0005] EP-A-0037696 describes an injection device with a simple plunger and ratchet mechanism by which the plunger is urged forwards on each actuation by a preset distance, thus dispensing a set dose. However, the syringe is fixed and the needle permanently projects from the forward end of the barrel. This requires the user to push the whole device in order to make the needle penetrate the flesh, which is often very difficult for a person self-administering an injection. It is preferable to have the needle 'fired' from a retracted position, as in DE 3638984.

[0006] The aim of this invention is an injection device capable of generating repeated doses from a syringe, in which the dose is pre-set into the construction of the device and there is no need for any adjustments. The device is simply primed and fired, the needle being projected and then the dose forced through it. The construction can therefore be very much simpler and straightforward than DE 3638984.

[0007] According to the present invention there is provided an injection device with an elongate barrel-like body for giving a sequence of injections of liquid from a capsule, the capsule being carried therein in a manner allowing longitudinal movement between limiting positions, and having a needle at one, forward end and a piston actuable through the other, rear end, the device comprising a plunger, to co-operate with the piston and which is actuable to cause emission of doses through the needle, spring drive means with a limited travel which, when energised, engages the plunger at a first position thereon and which, when released, urges it forwardly, the drive in a first phase carrying the capsule from a rear to a forward limit, by virtue of a substantial hydraulic lock, to project the needle from the body, and in a second phase forcing the piston alone on to eject a dose, manually operable priming means to re-energise the drive means, and means for releasably holding the spring drive means energised after priming, characterised in that the plunger has ratchet teeth and the drive means has a pawl to engage therewith positively in the drive direction, in that the capsule is mounted in a carrier capable of limited longitudinal movement within the body and having a pawl to engage the ratchet teeth, and in that there is a lost motion connection between the carrier and the drive means, the arrangement being such that the drive means, on being re-energised, withdraws the carrier with the capsule to its rear limit but, by virtue of the lost motion connection, withdraws the drive means further for its pawl to have its engagement with the teeth shifted to the rear, such that in the first phase of the drive stroke the capsule and its carrier are moved forwards together until arrested, and such that in the second phase of the drive stroke, the drive pawl continues to thrust the plunger forwards, the lost motion connection allowing relative movement between the drive means and the carrier, whereby the carrier pawl has its engagement with the teeth shifted to the rear.

[0008] Thus, on the forward stroke, the plunger first pushes the capsule forwards to its limit by acting on the liquid in the capsule which is effectively solid, and then carries on more slowly to eject one dose. The plunger is then stopped, but at a position further forward with respect to the capsule than before that operation. For the next dose, the priming means pulls back the plunger and capsule and reenergises the spring drive means, which is temporarily held by a trigger mechanism. But before it achieves this, the capsule carrier will reach its rearward limit, while the drive means has its relationship to the plunger adjusted to compensate for the emission of one dose. The device is then ready for the next injection.

[0009] Conveniently, the drive means includes a tubular member sleeved over the plunger with coil spring means encircling it and effectively reacting against the body. The priming means may simply be a knob on the end of the tubular member accessible at the rear end of the body.

[0010] The means for releasably holding the drive means may be a trigger device carried by the body and arranged to engage a detent on the tubular member

when that member is withdrawn rearwardly from the body to a predetermined extent. Preferably, it comprises diametrically opposed pads accessible outside the body and connected by springy webs within the body which encircle the tubular member to engage diametrically opposed detents on that member when withdrawn. Squeezing of the pads together causes the webs to diverge and release from the detents. Conveniently, the or each detent has a snap action engagement with the trigger when the tubular member reaches its predetermined withdrawn position.

[0011] For a better understanding of the invention, one embodiment will now be described, by way of example, with reference to the accompanying drawings, in which:

Figure 1 is an axial section of an injection device,
Figure 2 is a cross section on the line II-II of Figure 1,
Figure 3 is an axial section, to an enlarged scale, of part of the device of Figure 1, the sectional plane being at right angles to that of Figure 1,
Figure 4 is a detail of a lost motion coupling also shown in Figure 3,
Figure 5 shows further axial sections of the device in various stages of operation, and
Figure 6 shows side views of the device in various stages of operation.

[0012] The device has a cylindrical barrel 1 comprising two tubes 2 and 3 with a telescoped joint. Within the forward, longer cylindrical tube 2 there is a co-axial sleeve 4 inside which is carried a capsule 5 containing the liquid to be injected. It has a piston 6 initially near its rear end when the capsule is full, and its forward end has a neck fitted with a cap 7 which seals the capsule by a membrane and which locates within a reduced forward end portion of the sleeve 4. A needle assembly 8 can be screwed over this reduced forward end and, when fully fitted, the rear end of the needle penetrates the membrane to open a very fine passage for the liquid in the capsule through the needle.

[0013] The needle assembly 8 is largely shrouded by a cylindrical insert 9 which plugs into the forward end of the tube 2. When the needle is retracted, as shown in Figure 1, the tip is within this insert 9, but when the device is fired as will be described later, the needle will project proud of the insert 9. The extent of this projection, and hence the depth to which the needle will penetrate, may be determined by the setting of the insert 9. As shown in Figure 1, it plugs fully into the tube 2, giving a maximum projection of the needle when used. But it could be removed, rotated and plugged in again, and with appropriate formations, such as co-operating grooves and ribs, it may then be set to extend the barrel 1 slightly, and thus reduce the amount of needle penetration. As seen in Figure 6, the tube 2 has an elongate window 10 in which part of the insert 9 will appear, and this may have a marking to indicate, in millimetres for example, the amount of penetration given by that setting.

[0014] The piston 6 abuts a rearwardly extending rod 11 which is formed with ratchet teeth 12, their pitch corresponding to the dosage delivered by one actuation of the device. The steep, abutment faces of the ratchet teeth face rearwardly and are engaged by two sets of pawls. One set of pawls 13 incline forwardly and inwardly from a cage-like formation at the rear end of the sleeve 4. This terminates in a disc 14 centrally apertured for free passage of the rod 11 and of larger diameter than the main body of the sleeve 4 so that it provides an outer annular rib 15 whose forward face initially abuts against an internal rib 16 of the tube 2. These ribs 15 and 16 and the interior of the insert 9 maintain the sleeve 4 co-axial with the barrel 1.

[0015] Extending further rearwardly from the disc 14 there are two parallel diametrically opposed fingers 17 with outwardly projecting studs 18 at their free ends. These engage in slots 19 in associated parallel legs 20 which alternate circumferentially with the pawls 21 of the other set engaging the teeth 12. The legs 20 and pawls 21 extend forwardly from an annular flange 22 at the forward end of a tube 23 which sleeves over the rod 11 and which has a priming knob 24 at its rear end, beyond the barrel 1. At an intermediate point of the tube 23 there are diametrically opposed external abutments 25 in the form of saw teeth with the sloping sides facing rearwardly and the steep sides facing forwardly.

[0016] Near the rear end of the tube 3 there is a release mechanism 26. This comprises two diametrically opposed pads 27 located within apertures in the tube 3 and connected by resilient, flexible webs 28 which spread to embrace the tube 23. These pads 27 are normally proud of the exterior of the tube 3. Between the rear face of the flange 22 and this release mechanism 26 there is a coil spring 29 surrounding the tube 23.

[0017] For use, it will be assumed that the insert 9 will be fitted at the appropriate setting and that a needle cover 30, which is usually provided as shown in Figure 6, has been removed. The device is then in the condition as shown at A in Figure 5 and C in Figure 6 with the ribs 15 and 16 abutting, the spring 29 extended and relaxed, and the studs 18 at the rear ends of the slots 19.

[0018] The user primes the device by grasping the barrel 1 in one hand and pulling the knob 24 by the other. The sleeve 4 has very little resistance to rearward movement from its initial position and, by virtue of the pawls 21 at least, the tube 23 does exert some grip on the rod. Therefore, pulling the knob 24 also draws back the rod 11 and that, acting through the pawls 13, carries the sleeve 4 and the capsule 5 with it. Thus the tip of the needle is withdrawn within the insert 9. This position is shown at B in Figure 5 and D in Figure 6.

[0019] The rearward movement of the sleeve 4, the capsule 5 and the rod 11 is limited by the rib 15 coming

up against the forward end 31 of the tube 3. However, the tube 23 can continue by virtue of the lost motion mechanism provided by the studs 18 and the slots 19, and as it does so the abutments 25 which have wedged between the webs 28 pass to the rear of the release mechanism 26 as shown at C in Figure 5, and in Figure 1. This extra movement of the tube 23 means that the pawls 21 click over one pair of teeth 12 on the rod 11.

[0020] In the event of any resistance to the free rearward movement of the sleeve 4, the tube 23 will at first move independently. But the lost motion connection will ensure that, after it has travelled the pitch of one pair of teeth 12, the sleeve 4 will follow, and will reach its rearward limit as the abutments 25 snap past the webs 28. Thus the relative displacement between the pawls 13 and the pawls 21 is limited to a distance equal to the pitch of one pair of teeth 12.

[0021] In any event, whatever the sequence of movement of the sleeve 4 and the tube 23, the device is now primed.

[0022] For the actual injection, the insert 9 is held against the user's skin, and the pads 27 are squeezed. This spreads the webs 28 sufficiently for them radially to clear the abutments 25. The spring 29 can now exert itself and push the tube 23 forwards. By the engagement of the pawls 21 with the rod 11, the latter is also pushed forwards. Since, by virtue of the liquid in the capsule 5 and the very fine bore of the needle, the piston 6 is virtually solid with the capsule, the first effect is for the piston to carry the sleeve 4 and capsule 5 forwards, projecting the needle. But this movement is arrested when the ribs 15 and 16 re-engage. This is shown at D in Figure 5. But there is still scope for further movement of the tube 23, and the spring 29 now pushes the piston 6 alone, via the pawls 21 and the rod 11, until the rear ends of the slots 19 come up against the now stationary studs 18 and/or the flange 22 abuts against an internal shoulder 32 of the tube 3. This movement forces out a measured dose from the capsule 5. During this second phase the pawls 13 click over one pair of teeth and so the device is then in its original condition, except that the pawls 13 and 21 each engage the pairs of teeth 12 one further back from the pairs previously engaged.

[0023] Further injections can be carried out by the same process and it will be seen that the same dose will be administered each time, corresponding to the pitch of the teeth 12.

[0024] The ratchet teeth 12 may be annular so that it will not matter how the capsule 5 is rotationally positioned. Alternatively, and as illustrated in Figures 2 and 3, they may form sunken racks along diametrically opposite sides of the rod 11. The pawls will thus be confined by the shoulders along the sides of the racks and prevent the parts that move longitudinally of the barrel 1 mutually rotating. However, with separate, diametrically opposed abutments 25, provision may be made to stop this assembly as a whole rotating. If the tube 23 was twisted by the knob 24 from the Figure 2 position, it could release the &butments 25 from the webs 28. The flange 22 could have one or more lugs engaged in longitudinal grooves on the inside of the tube 3, for example. Alternatively, the abutments 25 could be combined into an annular, tooth-sectioned rib so that twisting the knob 24 would have no effect.

Claims

1. An injection device with an elongate barrel-like body (1) for giving a sequence of injections of liquid from a capsule (5), the capsule (5) being carried therein in a manner allowing longitudinal movement between limiting positions, and having a needle (8) at one, forward end and a piston (6) actuable through the other, rear end, the device comprising a plunger (11), to cooperate with the piston (6) and which is actuable to cause emission of doses through the needle (8), spring drive means (23,29) with a limited travel which, when energised, engages the plunger (11) at a first position thereon and which, when released, urges it forwardly, the drive in a first phase carrying the capsule (5) from a rear to a forward limit, by virtue of a substantial hydraulic lock, to project the needle (8) from the body, and in a second phase forcing the piston (6) alone on to eject a dose, manually operable priming means (24) to re-energise the drive means (23,29), and means (25,28) for releasably holding the spring drive means (23,29) energised after priming, characterised in that the plunger (11) has ratchet teeth (12) and the drive means (23,29) has a pawl (21) to engage therewith positively in the drive direction, in that the capsule (5) is mounted in a carrier (4) capable of limited longitudinal movement within the body and having a pawl (13) to engage the ratchet teeth (12), and in that there is a lost motion connection (18,19) between the carrier (4) and the drive means (23,29), the arrangement being such that the drive means, on being re-energised, withdraws the carrier (4) with the capsule (5) to its rear limit but, by virtue of the lost motion connection (18,19), withdraws the drive means (23,29) further for its pawl (21) to have its engagement with the teeth (12) shifted to the rear, such that in the first phase of the drive stroke the capsule (5) and its carrier (4) are moved forwards together until arrested, and such that in the second phase of the drive stroke, the drive pawl (21) continues to thrust the plunger (11) forwards, the lost motion connection (18,19) allowing relative movement between the drive means (23,29) and the carrier (4), whereby the carrier pawl (13) has its engagement with the teeth (12) shifted to the rear.

2. An injection device as claimed in Claim 1, characterised in that the drive means (23,29) includes a

tubular member (23) sleeved over the plunger (11) with coil spring means (29) encircling it and effectively reacting against the body (1).

3. An injection device as claimed in Claim 2, characterised in that the priming means is a knob (24) on the end of the tubular member (23) accessible at the rear end of the body (1).

4. An injection device as claimed in Claim 2 or 3, characterised in that the means (25,28) for releasably holding the drive means (23,29) is a trigger device (26) carried by the body (1) and arranged to engage a detent (25) on the tubular member (23) when that member is withdrawn rearwardly from the body to a predetermined extent.

5. An injection device as claimed in Claim 4, characterised in that the trigger device (26) comprises diametrically opposed pads (27) accessible outside the body (1) and connected by springy webs (28) within the body which encircle the tubular member (23) to engage diametrically opposed detents (25) on that member when withdrawn, squeezing of the pads (27) together causing the webs (28) to diverge and release from the detents (25).

6. An injection device as claimed in Claim 4 or 5, characterised in that the or each detent (25) has a snap action engagement with the trigger device (26) when the tubular member (23) reaches its predetermined withdrawn position.

Patentansprüche

1. Injektionsgerät mit einem länglichen Zylinder (1) zur Abgabe einer Folge von Injektionen von Flüssigkeit aus einer Kapsel (5), die in dem Zylinder derart angeordnet ist, daß sie eine Längsbewegung zwischen Endlagen ausführen kann und die eine Nadel (8) am vorderen Ende und einen Kolben (6) aufweist, der durch das hintere Ende hindurch betätigbar ist, einem Stößel (11), der mit dem Kolben (6) zusammenwirkt und betätigbar ist, um die Ausgabe von Dosen durch die Nadel (8) zu bewirken, einem Federantrieb (23,29) mit einem begrenzten Weg, der im gespannten Zustand an dem Stößel (11) an einer ersten Position anliegt und beim Freigeben den Stößel (11) vorschiebt, wobei der Federantrieb in einer ersten Phase die Kapsel (5) durch eine im wesentlichen hydraulische Verriegelung von einer hinteren zu einer vorderen Endlage bewegt, um die Nadel (8) aus dem Zylinder herauszuschieben, und in einer zweiten Phase nur den Kolben (6) vorschiebt, um eine Dosis auszugeben, einer manuell betätigbaren Vorspanneinrichtung (24) zum Wiederspannen des Federantriebes (23,29) und einer Vorrichtung (25,28) zum auslösbaren Halten des wieder gespannten Federantriebes (23,29)
dadurch gekennzeichnet, daß der Stößel (11) Sperrzähne (12) hat und der Federantrieb (23,29) eine mit diesen in der Antriebsrichtung formschlüssig zusammenwirkende erste Sperrklinke (21) aufweist, daß die Kapsel (5) in einem Träger (4) angeordnet ist, der eine begrenzte Längsbewegung in dem Zylinder ausführen kann und eine zweite, in die Sperrzähne (12) eingreifende Sperrklinke (13) aufweist, und daß zwischen dem Träger (4) und dem Federantrieb (23,29) eine Totgangverbindung (18,19) vorgesehen ist, wobei die Anordnung derart ist, daß beim Wiederspannen des Federantriebs der Träger (4) mit der Kapsel (5) in seine hintere Endlage, der Federantrieb (23,29) jedoch aufgrund der Totgangverbindung (18,19) weiter zurückgezogen wird, damit die erste Sperrklinke (21) ihren Eingriff mit den Zähnen (12) nach rückwärts verschiebt, derart, daß in der ersten Phase des Antriebshubes die Kapsel (5) und ihr Träger (4) zusammen vorwärts bewegt werden, bis sie arretiert sind, und in der zweiten Phase des Antriebshubes die erste Sperrklinke (21) fortfährt, den Stößel (11) vorzuschieben, wobei die Totgangverbindung (18,19) eine Relativbewegung zwischen dem Federantrieb (23,29) und dem Träger (4) zuläßt und der Eingriff der zweiten Sperrklinke (13) mit den Zähnen (12) nach rückwärts geschoben wird.

2. Injektionsgerät nach Anspruch 1, dadurch gekennzeichnet, daß der Federantrieb (23) ein über den Stößel (11) geschobenes Rohr (23) und eine auf diesem Rohr angeordnete Schraubenfeder (29) aufweist.

3. Injektionsgerät nach Anspruch 2, dadurch gekennzeichnet, daß die Vorspanneinrichtung ein Knauf (24) am Ende des Rohres (23) ist, der am hinteren Ende des Zylinders (1) zugänglich ist.

4. Injektionsgerät nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß die Vorrichtung zum lösbaren Halten des Federantriebes (23,29) eine Ausösevorrichtung (26) ist, die in dem Zylinder (1) so angeordnet ist, daß sie mit einer Sperrnase (25) an dem Rohr (23) zusammenwirkt, wenn das Rohr um einen vorbestimmten Betrag nach rückwärts aus dem Zylinder herausgezogen ist.

5. Injektionsgerät nach Anspruch 4, dadurch gekennzeichnet, daß die Auslösevorichtung (26) diametral gegenüberliegende Drücker (27) aufweist, die von außen zugänglich und miteinander durch federnde Stege (28) verbunden sind, welche innerhalb des Zylinders (1) angeordnet sind und das Rohr (23) umgeben und in diametral gegenüberliegende

Sperrnasen (25) an dem Rohr eingreifen, wenn dieses zurückgezogen wird, wobei durch Zusammendrücken der Drücker (27) die Stege (28) gespreizt werden und von den Sperrnasen (25) freikommen.

6. Injektionsgerät nach Anspruch 4 oder 5, dadurch gekennzeichnet, daß die bzw. jeder Sperrnase (25) in Schnappeingriff mit der Auslösevorrichtung (26) ist, wenn das Rohr (23) seine vorbestimmte zurückgezogene Stellung erreicht.

Revendications

1. Dispositif d'injection ayant un long corps de type cylindre (1) pour donner une séquence d'injections de liquide à partir d'une capsule (5), la capsule (5) y étant portée d'une manière qui lui permet de se déplacer dans la direction longitudinale entre des positions limites, et ayant une aiguille (8) à une extrémité, avant, et un piston (6) actionnable par l'autre extrémité, arrière, le dispositif comprenant un plongeur (11), destiné à coopérer avec le piston (6) et qui peut être actionné de façon à provoquer l'émission de doses au travers de l'aiguille (8), un moyen d'entraînement à ressort (23, 29) ayant une course limitée, qui, lorsqu'il est activé, entre en prise avec le plongeur (11) en une première position sur ce dernier, et qui, lorsqu'il est relâché, le pousse vers l'avant, l'entraînement transportant, dans une première phase, la capsule (5) depuis une limite arrière vers une limite avant, à l'aide d'un verrou hydraulique substantiel, pour faire saillir l'aiguille (8) du corps, et, dans une deuxième phase, poussant le piston (6) tout seul pour éjecter une dose, un moyen d'amorçage (24) actionnable à la main pour réactiver le moyen d'entraînement (23, 29), et un moyen (25, 28) pour maintenir de manière dégageable le moyen d'entraînement à ressort (23, 29) activé après l'amorçage, caractérisé par le fait que le plongeur (11) possède des dents d'encliquetage (12) et le moyen d'entraînement (23, 29) a un cliquet (21) destiné à entrer en prise avec ces dernières, de manière positive dans le sens de l'entraînement, par le fait que la capsule (5) est montée dans un porteur (4) capable d'avoir un déplacement longitudinal limité dans le corps et ayant un cliquet (13) destiné à entrer en prise avec les dents d'encliquetage (12), et par le fait qu'il y a une liaison à course morte (18, 19) entre le porteur (4) et le moyen d'entraînement (23, 29), l'arrangement étant tel que le moyen d'entraînement, lorsqu'il est ré-activé, tire le porteur (4) avec la capsule (5) vers sa limite arrière mais, du fait de la liaison à course morte (18, 19), tire le moyen d'entraînement (23, 29) davantage de telle sorte que l'engagement de son cliquet (21) avec les dents (12) soit décalé vers l'arrière, de sorte que, dans la première phase de la course d'entraînement, la capsule (5) et son porteur (4) soient déplacés ensemble vers l'avant jusqu'à ce qu'ils soient arrêtés, et de sorte que, dans la deuxième phase de la course d'entraînement, le cliquet d'entraînement (21) continue à pousser le plongeur (11) vers l'avant, la liaison à course morte (18, 19) permettant un déplacement relatif entre le moyen d'entraînement (23, 29) et le porteur (4), en conséquence de quoi l'engagement du cliquet (13) du porteur avec les dents (12) est décalé vers l'arrière.

2. Dispositif d'injection selon la revendication 1, caractérisé par le fait que le moyen d'entraînement (23, 29) comprend un élément tubulaire (23) gainé sur le plongeur (11) avec un moyen à ressort à boudin (29) qui l'entoure et réagit de manière efficace à l'encontre du corps (1).

3. Dispositif d'injection selon la revendication 2, caractérisé par le fit que le moyen d'amorçage est un bouton (24) placé à l'extrémité de l'élément tubulaire (23) accessible à l'extrémité arrière du corps (1).

4. Dispositif d'injection selon la revendication 2 ou 3, caractérisé par le fait que le moyen (25, 28) destiné à maintenir le moyen d'entraînement (23, 29) de manière dégageable est un dispositif de déclenchement (26) porté par le corps (1) et conçu de façon à entrer en prise avec une détente (25) aménagée sur l'élément tubulaire (23) lorsque cet élément est tiré du corps vers l'arrière sur une étendue prédéterminée.

5. Dispositif d'injection selon la revendication 4, caractérisé par le fait que le dispositif de déclenchement (26) comprend des patins diamétralement opposés (27) qui sont accessibles à l'extérieur du corps (1) et qui sont raccordés par des bandes élastiques (28) situées à l'intérieur du corps, qui entourent l'élément tubulaire (23) de façon à entrer en prise avec les détentes diamétralement opposées (25) aménagées sur cet élément, lorsqu'il est tiré, le fait de coincer les patins (27) ensemble entraînant les bandes (28) à diverger et à se dégager des détentes (25).

6. Dispositif d'injection selon la revendication 4 ou 5, caractérisé par le fait que la ou chaque détente (25) entre en prise de manière immédiate avec le dispositif déclencheur (26) lorsque l'élément tubulaire (23) atteint sa position tirée prédéterminée.

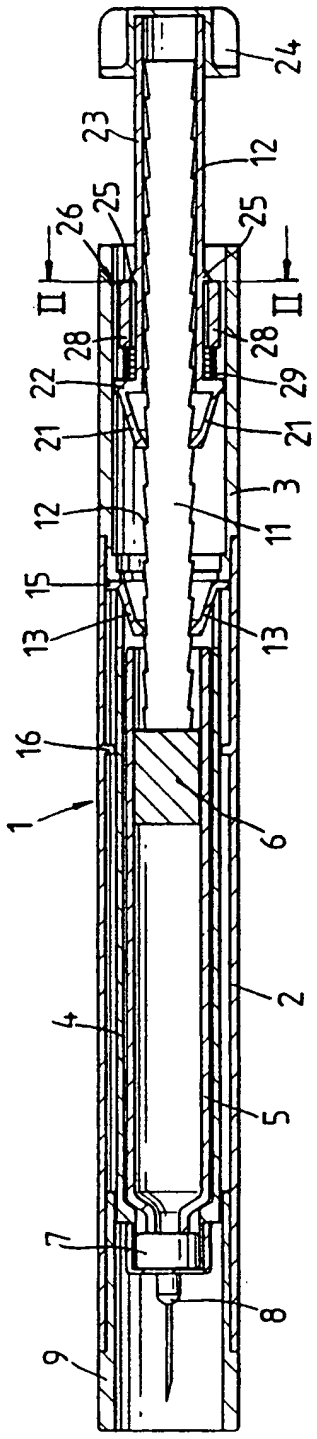


Fig. 1

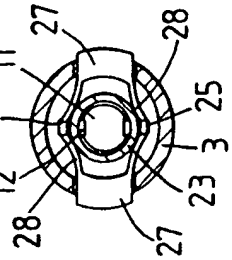


Fig. 2

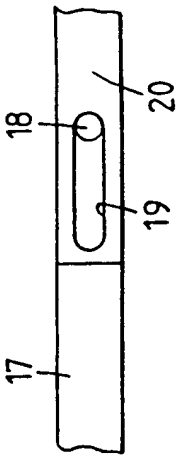
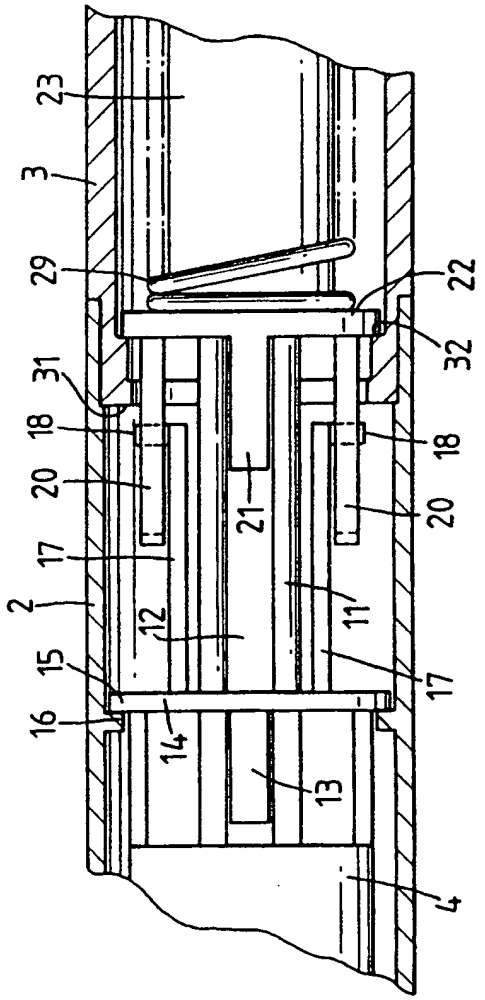


Fig. 4



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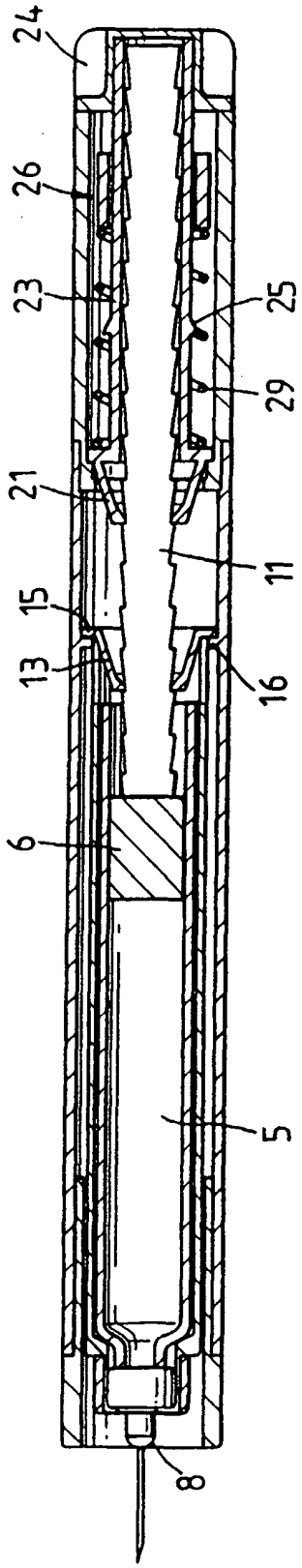


Fig. 5A

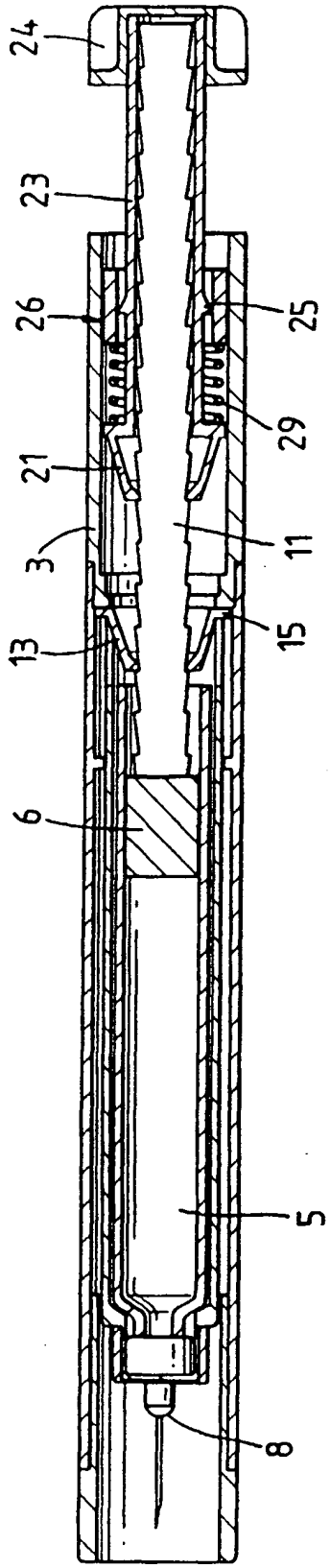


Fig. 5B

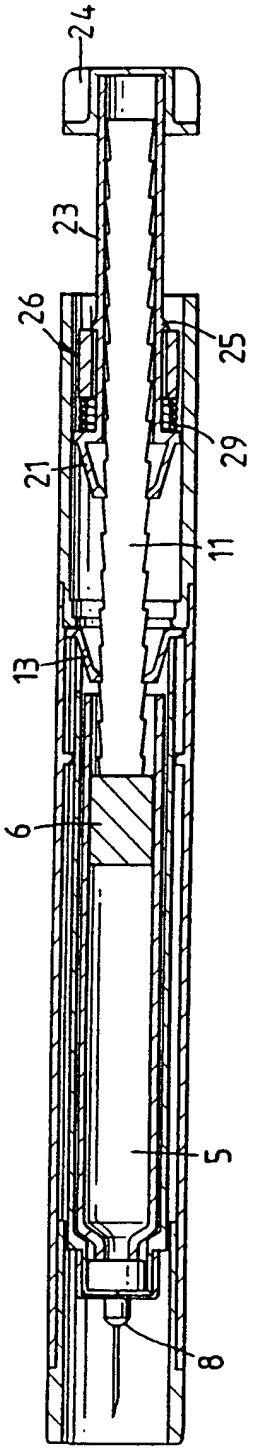


Fig. 5C

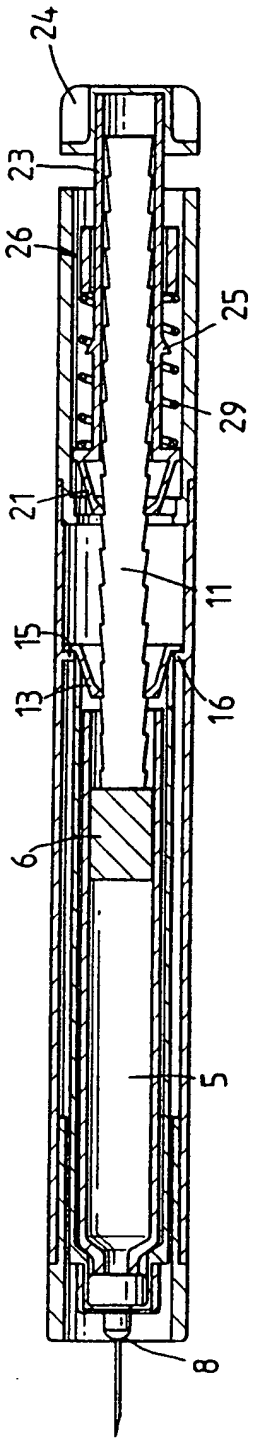


Fig. 5D

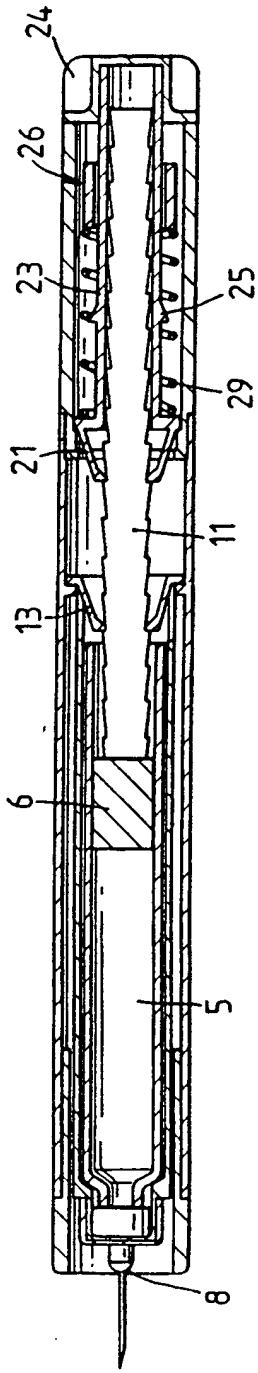


Fig. 5E

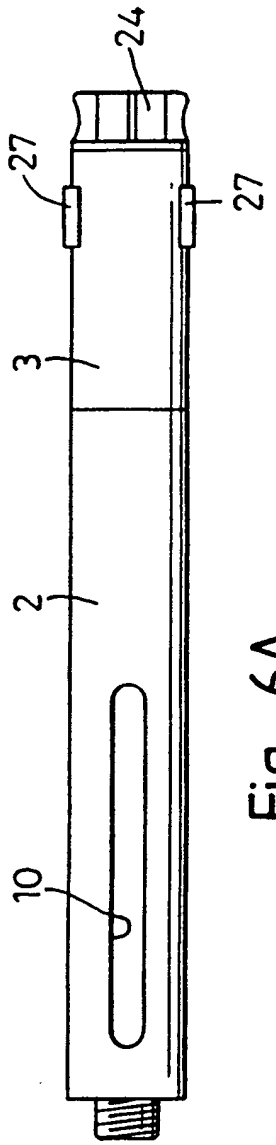


Fig. 6A

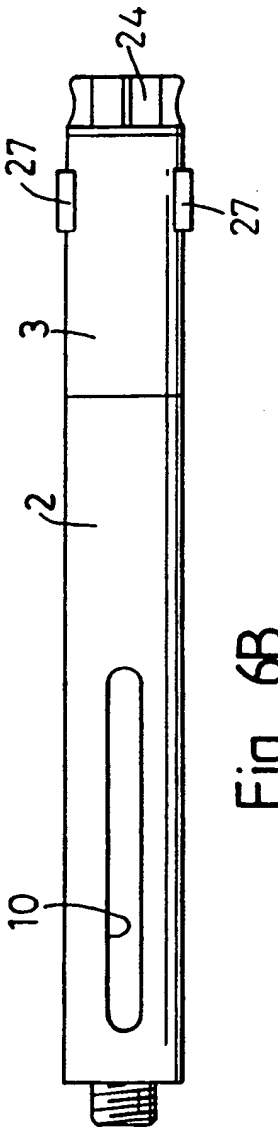


Fig. 6B

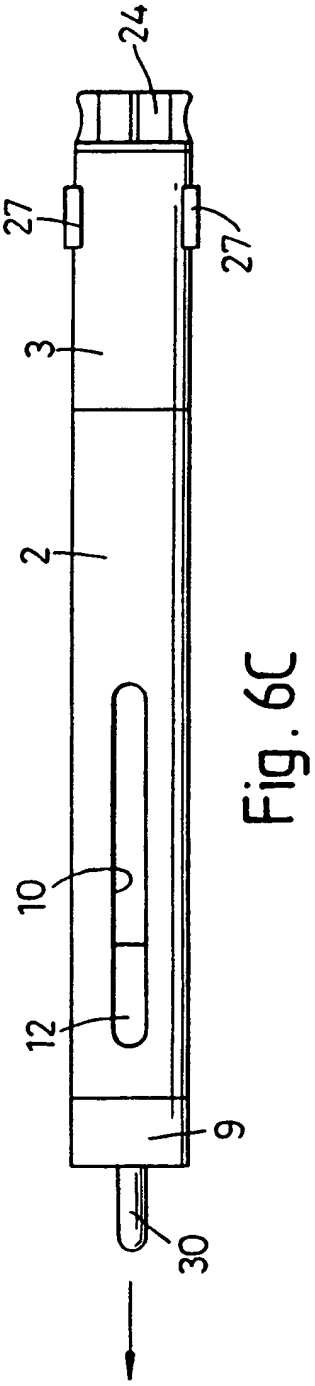
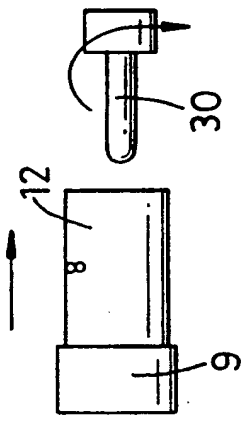


Fig. 6C



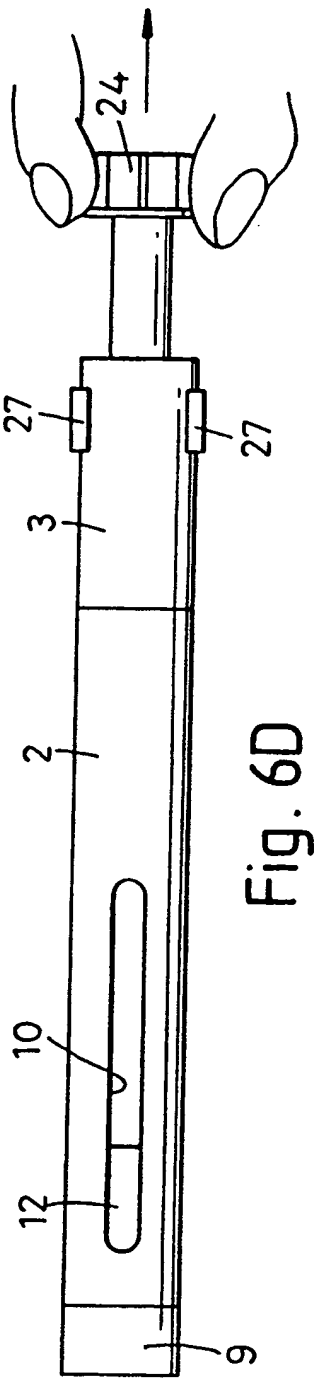


Fig. 6D

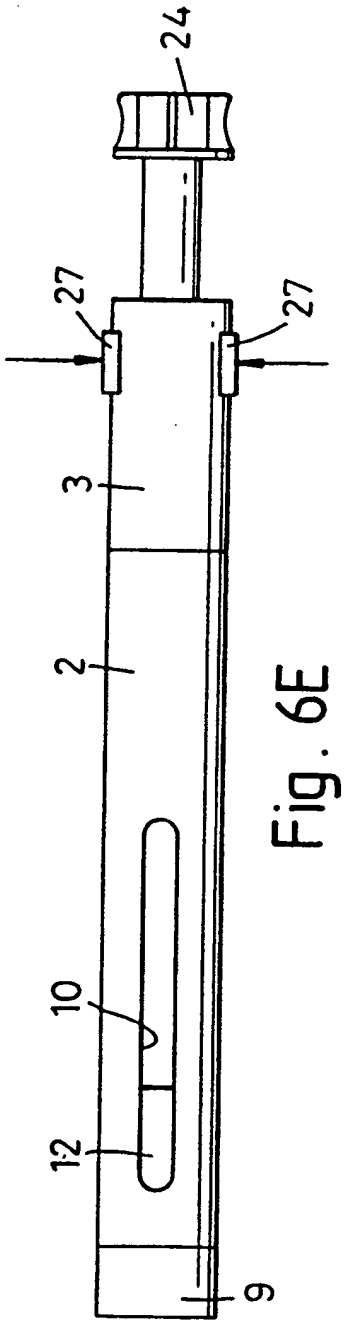


Fig. 6E

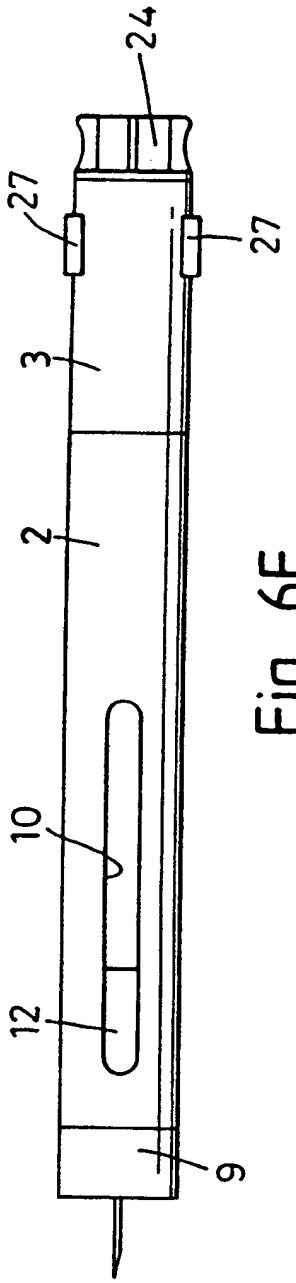


Fig. 6F

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